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Dr. Ruth Lunn
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Subject:
Expert Panel Report and Listing Recommendation for Cobalt-Tungsten Carbide Powders and Hard Metals

Date:
27 March 2009

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B0078028

Dear Dr. Lunn:

On February 11, 2009, the National Toxicology Program (NTP) published in the Federal Register (Volume 74, Number 27) the availability of, and request for comment on, the Expert Panel's recommendation with respect to the listing status for cobalt-tungsten carbide powders and hard metals and its scientific justification for that recommendation. Working together with the Health, Safety & Environment Committee of the International Tungsten Industry Association (ITIA), ARCADIS has developed comments on the Expert Panel's listing recommendation and scientific justification for that recommendation (Expert Panel report Part B). The term "hardmetal" is used herein unless citing specific literature or language from the Expert Panel report, as it is synonymous with "hard metal".

The ITIA is registered under Belgian law as a not-for-profit association with scientific purposes in support of the tungsten industry. ITIA's members are based in 17 countries (including the U.S) and include mining companies, processors/consumers, trading companies and assayers, as well as the world's leading manufacturers, importers, and users of hardmetal.

SUMMARY OF COMMENTS ON THE DRAFT BACKGROUND DOCUMENT

This letter provides technical comments developed and submitted on behalf of the ITIA with regard to the Expert Panel's *Recommendation for Listing Status for Cobalt-*

Tungsten Carbide Powders and Hard Metals and Scientific Justification for the Recommendation (Expert Panel Report Part B). The primary concerns with the listing and supporting data are as follows: the recommendation encompasses too wide of a range of materials and the toxicity data only cover a limited group of cobalt-tungsten carbides; the genotoxicity and carcinogenicity data used to justify the listing recommendation are primarily for soluble cobalt and tungsten compounds and do not support the listing of cobalt-tungsten carbide powders and hardmetal; and the epidemiological data used to support the listing are weak and inconclusive. These concerns are described in further detail below in connection with specific statements contained in Part B of the Expert Panel Report.

The Recommendation Encompasses too Wide of a Range of Materials

1. **Overall Evaluation section: Report states "*It was suggested by the panel that the title of the nomination be changed to 'Powders and Hard Metals of Cobalt-Tungsten Carbide.*"**

   Comment: The recommended change to the title acknowledges that there are differences in properties between hardmetals as a class and those hardmetals containing cobalt. However, even the suggested reduction in scope does not sufficiently limit the listing to those substances for which data are available, since the *in vivo* and *in vitro* data are almost exclusively cover unsintered cobalt-tungsten carbides with a narrow range of constituents.

   Having data for all of the major types of materials included in the listing is especially important because hardmetals of cobalt-tungsten carbides do not have well-defined compositions. Instead, they include a range of compositions with an associated range of physical-chemical properties. These properties (e.g., corrosion resistance) likely affect toxicity and carcinogenicity more specifically, with different toxicological properties associated with the different compositions.

Worker populations likewise are potentially exposed to a wide range of hardmetal formulations with varying properties. This range of exposures adds to the uncertainty when interpreting the hardmetal epidemiological studies. Such uncertainties have never been addressed by the study authors or by the Expert Panel.

The title of the listing recommendation should therefore be limited to the compositions for which there are data; specifically, unsintered powders of tungsten carbide with 6% to 10% cobalt and no auxiliary metals or metal carbides.

2. **Section 2.4 Effect of sintering: Report states "*These findings are suggestive of higher risk among workers exposed only to unsintered materials, but the data are insufficient to support firm conclusions.*"**

   Comment: The Expert Panel acknowledged the potential importance of sintering by noting that the epidemiological data and IARC suggested a decreased risk associated with exposure to sintered materials. IARC concluded that no increased risk of lung cancer was identified for exposure to sintered hardmetal (IARC, 2006, p. 130; NTP, 2008, p.56). Given that the majority of the *in vivo* and *in vitro* data on cobalt-tungsten carbides were conducted on unsintered materials, any classification should be limited to the unsintered materials. While the effect of sintering is not currently known, the available evidence suggests that it changes the properties of the material.

The Genotoxicity and Carcinogenicity Data are Primarily for Soluble Cobalt and Tungsten Compounds and Do Not Support the Listing of Cobalt-Tungsten Carbide Powders and Hardmetal

1. **Overall Evaluation section: Report states "*Cobalt-tungsten carbide releases substantial amounts of cobalt ions in both in vivo and in vitro studies. Clear evidence of carcinogenicity of soluble cobalt compounds***

from animal studies and compeling animal and in vitro data of genotoxicity were major factors for the assessment . . ."

Comment: The recommendation to list hardmetal as "reasonably anticipated to be a carcinogen" is largely based on data for soluble cobalt. Because the listing recommendation is for cobalt-tungsten carbide powders and hard metals, the data to support this recommendation should instead relate primarily to cobalt-tungsten powders and hard metals.

However, there are no *in vivo* carcinogenicity data for cobalt-tungsten carbide powders or hardmetals. This is of particular concern because the Background Document specifies that these materials have "unique toxicological properties", and thus the use of data covering other substances to support the listing is very questionable. Furthermore, while *in vitro* and *in vivo* studies have demonstrated that cobalt tungsten carbides release cobalt ions, the rate and effect of such release is not the same as that for soluble cobalt compounds. Corrosion and subsequent solubilization of constituent metal ion are required, and these processes do not occur at the same rate and level as for water-soluble cobalt compounds.

A related issue is the multi-step extrapolation of soluble cobalt data applied to cobalt-tungsten carbides. Since elemental cobalt (cobalt metal) is the constituent in cobalt-tungsten powders and hardmetals, and not soluble cobalt compounds, the approach used to assess carcinogenicity of cobalt-tungsten carbides extrapolates soluble cobalt data to elemental cobalt and then to cobalt-tungsten carbides of varying compositions and metal ion release rates and amounts.

As noted by a representative from the Cobalt Development Institute during the public meeting, the NTP is now conducting a two year chronic toxicity assessment of cobalt metal powder (study details can be found on the NTP website: http://ntp.niehs.nih.gov/index.cfm?objectid=BCA86473-123F-7908-

7B898090E101E567). This acknowledgement of the need for data on a specific material, and not just its constituents, is the correct approach and should be adopted here as well, rather than simply relying on use of soluble cobalt compound data. A classification recommendation that relies so heavily on data from soluble cobalt appears premature, given that the NTP cobalt metal powder study will yield more definitive and relevant data on carcinogenicity. But even the use of cobalt metal data without good quality human or animal carcinogenicity data for cobalt-tungsten carbides is not sufficient to assess the carcinogenicity of cobalt-tungsten carbides.

In addition to the comments contained in Part B of the Expert Panel Report, Part A of the Report recommended several changes to the Background Document which include several additions of cobalt mechanistic (page 8, section 5.4) and genotoxicity (page 9, section 5.5.2) data. This information, in addition to the existing soluble cobalt animal carcinogenicity data, has been used in Part B of the document to justify the carcinogenicity listing for cobalt tungsten carbides and hardmetals. However, such information has not been made available for public comment with respect to the quality and relevancy of the additional data to evaluation of the carcinogenicity of cobalt-tungsten carbide powders and hard metals. Such an opportunity should be provided.

2. **Overall Evaluation section: Report states "*Cobalt ions act at a number of molecular cancer related targets based upon both in vivo and in vitro studies, to potentially induce tumors; the targets include . . . (5) activity as a tumor promoter and co-carcinogen*."**

Comment: In addition to the comment set forth above on the use of soluble cobalt data to assess the carcinogenicity of cobalt-tungsten carbides, there is insufficient scientific evidence to conclude that cobalt is a tumor promoter or co-carcinogen. A *tumor promoter* is defined as an agent that increases the tumorgenic response to a genotoxic carcinogen when administered after the carcinogen, but is not carcinogenic on its own. *Co-carcinogens* are agents that

increase the overall carcinogenic process (number of tumors, time to tumor) caused by a genotoxic carcinogen when administered together with the carcinogen.

There are no data available to demonstrate that cobalt is either a promoter or co-carcinogen, as these activities can only be demonstrated in animal bioassays. *In vitro* data can provide mechanistic data suggesting or lending support to a finding that these activities are occurring. However, as noted above, the definitions of these two terms require evidence that the agent produces an increase in tumors.

3. **Other Relevant Data section, 3. Other Related Information . . . : Report states "*Cobalt alone was carcinogenic is several animal species.*"**

   Comment: This statement should specify that the available data is for water-soluble cobalt compounds, since the current language implies that there are data for elemental cobalt. The difference in interpretation is significant because cobalt metal has different toxicological and physico-chemical properties than water-soluble cobalt compounds.

4. **Other Relevant Data section, 3. Other RelatedInformation . . . : Report states "*Tungstate ($WO4^{2-}$) was found to promote nitrosamine-induced mammary tumors in rats.*"**

   Comment: As already noted with respect to the use of soluble cobalt data for evaluating the carcinogenicity of cobalt-tungsten carbides, it is not appropriate to use soluble tungsten compound data in determining whether the tungstate promotes nitrosamine-induced mammary tumors. In addition, the single study that was identified (Wei et al., 1985) does not provide scientific support for the proposition.

   The study instead found conflicting results with respect to the role of tungstate in promoting nitrosamine-induced mammary tumors. Although the 125 day test

demonstrated that there was a significant increase in mammary tumors with concurrent exposure to nitrosamine and sodium tungstate as compared to nitrosamine alone, there was no significant increase in mammary tumors in the 198 day test when the results of exposure to the same materials were compared.

The Epidemiological Data for Listing Are Weak and Inconclusive

1. **Section 2.1 Overall findings: Report states "*Both multi-plant studies (Moulin et al. and Hogstedt and Alexandersson) found excess lung cancer relative to the general population in a cohort analysis; the standard mortality ratio (SMR) was about 1.3.*"**

   Comment: The Expert Panel Recommendation and the Background Document should include a discussion regarding the uncertainty associated with an SMR of only 1.3. The statement set forth above does not acknowledge that the SMR of 1.34 in the Hogstedt and Alexandersson study was not statistically significant (95% Confidence Interval (CI): 0.77-2.13). Even in the Moulin et al. study where the SMR reached the threshold of *statistical* significance (95% CI: 1.00 – 1.66), the biological relevance of this finding should be discussed. In sum, given the critical nature of this reported association, a discussion of the effect size should be included in the Expert Panel's analysis.

2. **Section 2.2 Exposure-response relationship: Report states "*There was evidence of an exposure-response relationship for lung cancer in these studies***
   - ***Moulin et al. reported statistically significant, increasing trends in ORs for duration of exposure at levels ≥ 2 and unweighted cumulative dose.*"**

   Comment: This statement does not accurately reflect the analysis of all data in the study. For the 3 categories of "Duration of exposure (levels ≥ 2)", the odds ratio (OR) goes from 1.61 (not significant) for ≤ 10 years, to 2.77 (significant) for

10-20 years, to 2.03 (not significant) for > 20 years. While the "Trend" was reported to be significant (p = 0.03), it's hard to understand how that could be accurate since the highest duration of exposure (> 20 yrs) was not significant, with a lower 95% CI of only 0.49. Instead, the actual results by duration of exposure do *not* demonstrate a dose-response relationship.

Also, the metric described as the "unweighted cumulative dose" is highly uncertain being calculated by exposure in terms of months in a particular job category times the exposure level for the job category. However, as discussed in detail in comments submitted by the ITIA in June, 2004, the "exposure level" as determined by the job-exposure matrix (JEM), is inherently inaccurate. Therefore, the unweighted cumulative dose is correspondingly inaccurate. For example, there is a total of only *five* air samples for the highest job-exposure levels (6-7), and job-exposure levels 8-9 had no air samples. In contrast, the lower exposure category used in the Moulin study (4-5) had a total of 130 independent air samples. It is also interesting to note that the maximum concentrations of cobalt in the two highest job-exposure categories with actual measurements (6-7) were over 2 times *lower* than the maximum concentration in categories 3 through 5. Thus, this metric cannot be used to establish a dose-response relationship between cobalt exposure and lung cancer.

In conclusion, since the major epidemiological studies included in the Expert Panel's *Recommendation for Listing Status* did not include a critical analysis of this exposure assessment, the statement set forth above is misleading.

3. **Section 2.2 Exposure-response relationship: Report states "[in Moulin et al.] *ORs for workers at the highest level of estimated exposure ranged from 2.03 to 4.13;*"**

Comment: The *Recommendation for Listing* should note that the OR range "for workers at the highest level of estimated exposure" was not statistically significant when the "Duration of exposure" equaled or exceeded 20 years. As

mentioned in the previous comment, the unweighted cumulative dose estimate of exposure is flawed and results in an exposure classification that is highly uncertain. The highest OR reported (4.13) was in the highest level estimated using the "unweighted cumulative dose" metric and thus is also suspect.

Without information about the lack of statistical significance and the uncertainty of some of the OR information, the statement set forth above is misleading and results in a mischaracterization of the dose-response for the purported association.

4. **Section 2.2 Exposure-response relationship: Report states "*Hogstedt and Alexandersson did not report consistent patterns of response with increases in the duration or estimated level of exposure in the Swedish cohort . . .*"**

   Comment: This information applies to Moulin et al. as well and should be provided in the discussion of.that study. As noted previously, Moulin et al. developed several metrics for magnitude and duration of exposure, and inconsistent findings were reported for each of them.

   There were 4 sub-categories in each of the following metrics: "Levels", "Duration of exposure", "Unweighted cumulative doses", and "Frequency-weighted cumulative doses." For each metric, only one of the sub-categories exhibited a statistically significant finding. Consequently, there was no clear dose-response relationship for any of these metrics; i.e., no consistent increase in the SMR with increased exposure.

5. **Section 3.1 Confounding: Report states "*However, the potential for confounding related to smoking and exposure to workplace lung carcinogens was addressed in the Moulin et al. study, which included measurements of ever vs. never smoking through interviews primarily with colleagues and relatives.*"**

Comment: "Ever vs. never" is not an appropriate way to describe the potential for smoking to confound the data with respect to lung cancer where studies have demonstrated a dose-response relationship between the incidence of lung cancer and the number of cigarettes smoked per day.

Moulin et al. noted that the only data "on this association [smoking and lung cancer] are the number of former smokers, although we do not know when each individual was coded as such", and characterized such data as "sketchy". This potential for misclassification could have a dramatic effect on confounding of the data due to smoking.

6. **Section 3.1.1 Smoking: Report states "*There was no evidence of confounding by smoking in the French cohort. Moulin et al. reported a crude OR of 2.29 versus a smoking-adjusted OR of 2.60 with overlapping CIs.*"**

Comment: This is not an accurate statement. Moulin et al. acknowledged that "the major possible confounder is smoking," and they further recognized that "in the case-control study, the risk associated with smoking (OR = 3.38) seemed lower than that expected." Similarly an OR of 2.60 is extremely low for smoking, as SMRs of over 20.0 have been reported in larger epidemiological investigations of cigarette smoking. Moulin et al. "acknowledge the possibility of misclassification, particularly among the nearly 20 percent of nonsmoking cases." These low ORs suggest that has occurred, and therefore the impact of confounding may be underestimated.

7. **Section 3.1.1 Smoking: Report states "*For the Swedish study, Hogstedt and Alexandersson reported that the proportion of current and former smokers in the Swedish cohort was similar to that of the national general population.*"**

Comment: The only elevated lung cancer mortality was from Factory A (SMR = 1.71), while Factory B (SMR = 0.84) and Factory C (SMR = 1.07) were not elevated. Interestingly, Factory A was the only urban facility, and Hogstedt and Alexandersson noted "the risk for lung cancer in the Stockholm municipality is approximately 30% higher than the national average." However, the authors used the national average to compute the SMR for Factory A. According to the Expert Panel's Report, the higher lung cancer rate in an urban setting such as the location of Factory A "only explains a small portion of the increased risk for lung cancer." But failure to apply the correct smoking group (urban smokers) for the Stockholm facility resulted in an inflated SMR for the Factory A. Use of the urban lung cancer rate would result in a SMR of less than 1.71, and potentially the lung cancer mortality would no longer be statistically significantly increased..

8. **Section 3.1.2 Other Occupational Carcinogens: Report states "*In further analyses of workers in one of the French plants, Wild reported a OR of 1.48 for exposure to any IARC carcinogen without considering exposure to cobalt-tungsten carbide.*"**

   Comment: The OR of 1.48 is higher than the SMR reported for lung cancer in the Moulin study. This suggests that there is a greater contribution to cancer mortality from sources other than cobalt-tungsten carbide.

9. **Section 4. Other Cancer Sites: Report states "*There was no evidence of exposure-response for cancers of the prostate or pancreas, and the leukemias occurred primarily in lower exposure categories (Tables 5 and 7, Hogstedt and Alexandersson).*"**

   Comment: In order to provide a conclusion for the data presented, a statement such as "suggesting these cancers were not related to hardmetal exposure" should be added.

CLOSING

We appreciate the opportunity to comment on these documents and are available to address any questions or concerns regarding the above comments.

Sincerely,

ARCADIS

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